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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/074,225 | 02/14/2002 | Fernando Donate | 38342-178463 | 6196 |

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MCKENNA LONG & ALDRIDGE LLP
1900 K STREET, NW
WASHINGTON, DC 20006

| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/074,225 | DONATE ET AL. | |
| | Examiner | Art Unit | |
| | David J Blanchard | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *2-4,16-48,50 and 51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5-15 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/6/04; 3/4/03;*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibits A-C*.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election with traverse of Group 1, claims 1, 5-6, 11-15 and 49 in part and claims 7-10 in the reply filed on 8/30/2004 is acknowledged. The traversal is on the grounds that the invention of Group 2, drawn to the same claims as Group 1, but including rabbit HPRG polypeptide (SEQ ID NO:6), which has the same functional attributes and it would be proper to rejoin Group 2 for initial examination. This is found persuasive and the restriction requirement between the inventions of Groups 1 and 2 is hereby WITHDRAWN. The restriction requirement between Groups 3-124 is maintained for reasons of record.

2. Claims 2-4, 16-48 and 50-51 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. Claims 1, 5-15 and 49 are under examination to the extent that the polypeptide or peptide comprise a human HPRG (SEQ ID NO:5) or rabbit HPRG (SEQ ID NO:6).

### *Claim Objections*

4. Claims 1, 5-7, 11-12 and 49 are objected to because of the following informalities:

Claims 1, 5-7, 11-12 and 49 are drawn to non-elected inventions.

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1, 5, 7-15 and 49 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which applicants regard as their invention.

a. Claims 1, 5, 7-15 and 49 are indefinite for reciting "human rabbit HPRG" in claim 1. Does the phrase "human rabbit HPRG" mean the human HPRG or the rabbit HPRG or is some human-rabbit hybrid HPRG contemplated by the phrase?

b. Claims 11 and 12 are indefinite for reciting "therapeutically effective amount" because it is unclear what the amount is intended for. The phrase is indefinite when the claims do not state the function, which is to be achieved. In re Frederiksen, 213 F2d 547, 102 USPQ 35 (CCPA 1954

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 5-15 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

There is insufficient written description encompassing "a sequence variant of SEQ ID NO:5 or SEQ ID NO:6 having substantially the same biologic activity of inhibiting angiogenesis, endothelial cell proliferation or endothelial tube formation" because the relevant identifying characteristics of the genus such as structure of other physical and/or chemical characteristics of "a sequence variant of SEQ ID NO:5 or SEQ ID NO:6" are not set forth in the specification as-filed, commensurate in scope with the claimed invention. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

With respect to a "sequence variant of SEQ ID NO:5 or SEQ ID NO:6 having substantially the same biologic activity of inhibiting angiogenesis, endothelial cell proliferation or endothelial tube formation", per the *Enzo* court's example of a description of an anti-inflammatory steroid couched "in terms of its function of lessening inflammation of tissues," which, the court stated, "fails to distinguish any steroid from others having the same activity or function," and which therefore, fails to satisfy the written-description requirement. Similarly, a "sequence variant of SEQ ID NO:5 or SEQ ID NO:6 having substantially the same biologic activity of inhibiting angiogenesis, endothelial cell proliferation or endothelial tube formation" does not distinguish the sequence variant from others having the same activity or function and as such does not satisfy the written-description requirement. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. The identity of the compound, and the description must convey what the compound is, and not just what it does.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112 first paragraph "written description" requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species; then the requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal register, Vol.

66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

9. Claims 1, 5-15 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated anti-angiogenic polypeptide or peptide having the sequence of the histidine-proline-rich (H/P) domain if human histidine-proline rich glycoprotein (HPRG) (SEQ ID NO:5) and the H/P domain of rabbit HPRG (SEQ ID NO:6) and an affinity ligand for binding to or isolating said human HPRG and said rabbit HPRG, does not reasonably provide enablement for sequence variants of human HPRG or sequence variants of rabbit HPRG or an affinity ligand for binding to or isolating human HPRG sequence variants or rabbit HPRG sequence variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity

of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to an isolated anti-angiogenic polypeptide or peptide having the H/P domain of human HPRG (SEQ ID NO:5) or the H/P domain of rabbit HPRG (SEQ ID NO:6) and sequence variants thereof, which broadly encompasses analogs, derivatives, fragments, and homologs of the human HPRG and rabbit HPRG, wherein the polypeptide or peptide or sequence variant is diagnostically or therapeutically labeled. The claims are also drawn to an affinity ligand useful for binding to or isolating a human HPRG or rabbit HPRG or sequence variant thereof. The specification teaches the human HPRG sequence and the rabbit HPRG sequence (see pages 11-14) and the HPRG and the H/P domain inhibit angiogenesis (see Examples). The specification discloses on pages 19-23 that fragments, analogs, or derivatives of the HPRG polypeptide would be amendable to functionally equivalent amino acid substitutions, however, this does not provide specific guidance that would enable one skilled in the art to make and use the invention without undue experimentation. The specification does not disclose the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species as in the case of analogs, derivatives, fragments or homologs.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar biological activity are

limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modifications in such proteins. The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does not disclose the following:

a. The general tolerance to modification and extent of such tolerance;

b. The specific positions and regions of the sequence which can be predictably modified and which regions are critical;

c. What fragments, if any, can be made which retain the biological activity of the intact protein; and

d. The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the

experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Furthermore, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987).

Lederman et al (Molecular Immunology 28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

Li et al (Proc. Natl. Acad. Sci. USA 77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other activities when constructing analogs (see entire document).

Although biotechnology has made great strides in the recent past, these references serve to demonstrate exactly how little we really know about the art. The art of protein chemistry remains very unpredictable as Burgess et al, Lazar et al, Schwartz et al, Lederman et al and Li et al conclusively demonstrate.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to producing and using the myriad of sequence variants of human HPRG and rabbit HPRG as encompassed by the scope of the claims, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

## *Claim Rejections - 35 USC § 102*

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Koide et al (Biochemistry, 25:2220-2225, 1986, Ids reference 3, filed 3/4/2003).

Claim 1 is drawn to an isolated anti-angiogenic polypeptide or peptide having the H/P domain of the human HPRG sequence (SEQ ID NO:5) or the rabbit HPRG (SEQ ID NO:6).

Koide et al teach the human HPRG polypeptide, which comprises a sequence that is identical to SEQ ID NO:5 (see the alignment attached to the back of this Office Action; Exhibit A) (see Figure 2). The term "having" is interpreted as open claim language meaning that the polypeptide or peptide "having" the sequence of human HPRG (SEQ ID NO:5) may contain additional sequence at the N- or C-terminus or both and therefore reads on the full-length human HPRG polypeptide taught by Koide et al. Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Thus, Koide et al anticipates the claim.

12. Claims 1, 11, 13 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Borza et al (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02). Claim 1 has been described supra. Claims 11 and 13 are drawn to an anti-angiogenic pharmaceutical composition comprising an effective amount of the H/P domain of the human or rabbit HPRG polypeptide and a pharmaceutically acceptable carrier and said pharmaceutical composition is in a form suitable for injection. Claim 49 is drawn to an

affinity ligand useful for binding to or isolating an HPRG-binding molecule comprising a human or rabbit HPRG polypeptide or peptide immobilized to a solid support or carrier.

Borza et al teach the rabbit HPRG polypeptide, which comprises a sequence that is identical to SEQ ID NO:6 (see the alignment attached to the back of this Office Action; Exhibit B) (see Figure 1). The term "having" is interpreted as open claim language meaning that the polypeptide or peptide "having" the sequence of rabbit HPRG (SEQ ID NO:6) may contain additional sequence at the N- or C-terminus or both and therefore reads on the full-length rabbit HPRG polypeptide taught by Borza et al. Borza et al also teach the human HPRG polypeptide (see Figure 2). Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Borza et al also teach the rabbit HPRG polypeptide in 0.1 M sodium phosphate buffer, pH 7.4, which is interpreted to be a pharmaceutically acceptable carrier and in suitable form for injection (see page 1926, left column). For this rejection the intended use as a pharmaceutical composition is given no patentable weight. See MPEP 2111.02. Further, Borza et al teach the rabbit HPRG polypeptide bound to a DEAE-cellulose column (solid support), which is an affinity ligand useful for binding to or isolating an HPRG-binding molecule. Thus, Borza et al anticipate the claims.

13. Claims 1, 5-15 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Simantov et al (US 2001/0041670 A1, 12/6/1999).

Claims 1, 11,13 and 49 have been described supra. Claims 5-10, 12 and 14-15 are drawn to a diagnostically and therapeutically labeled anti-angiogenic polypeptide or peptide comprising the H/P domain of the human or rabbit HPRG polypeptide (SEQ ID Nos:5 or 6, respectively), which is diagnostically or therapeutically labeled and a diagnostically acceptable carrier and a therapeutic anti-angiogenic pharmaceutical composition comprising said H/P domain of the human or rabbit HPRG polypeptide, which is bound to a therapeutically active moiety; and a pharmaceutically acceptable carrier.

Simantov et al teach the entire 525 amino acid sequence of human HPRG (i.e.,Genbank accession no. P04196) (see Exhibit C, residues 350-497), which is a polypeptide having the sequence of the H/P domain of human HPRG (SEQ ID NO:5) and HPRG binds with high affinity to thrombospondin-1 (TSP-1) (see page 1, left column). The term "having" is interpreted as open claim language meaning that the polypeptide or peptide "having" the sequence of human HPRG (SEQ ID NO:5) may contain additional sequence at the N- or C-terminus or both and therefore reads on the full-length human HPRG polypeptide taught by Simantov et al. Simantov et al teach HPRG immobilized on 96-well strips in solid phase binding assays, which is an affinity ligand useful for binding to or isolating an HPRG-binding molecule (i.e., TSP-1) (see page 12, paragraph [0164]). Simantov et al teach pharmaceutical compositions comprising a TSP-1 binding motif of HPRG (i.e., HPRG polypeptide) and a

pharmaceutically acceptable carrier (also interpreted as a diagnostically acceptable carrier) (see page 3, paragraphs [0039-0040] and page 6 paragraph [0084]). Simantov et al teach labeled TSP-1 binding proteins (i.e., HPRG) as probes and labels including radionuclides, fluorescein, rhodamine, Texas red and phycoerythrin as well as others (see page 10 and page 13, paragraph [0174]).

Products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

14. Claims 1, 5-15 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by Olsson et al (US 2002/0165131 A1, 2/5/2001) as evidenced by Koide et al (Biochemistry, 25:2220-2225, 1986, Ids reference 3, filed 3/4/2003) and as evidenced by Borza et al (Biochemistry, 35:1925-1934, 1996, Ids reference #2, filed 6/6/02).

The claims have been described supra.

Olsson et al teach an anti-angiogenic pharmaceutical composition comprising an HPRG polypeptide and a pharmaceutically acceptable carrier and the HPRG polypeptide may be the human HPRG or rabbit HPRG, which are polypeptides having the H/P domain of human or rabbit HPRG (SEQ ID Nos:5 and 6, respectively) as evidenced by Koide et al and Borza et al (see page 1, paragraphs [0009], [0005], [0034] and [0043] and exhibits A and B attached to the back of this Office Action). Olsson et al

teach effective amounts of the pharmaceutical compositions comprising the HPRG polypeptide (see page 5). Olsson et al teach that the HPRG polypeptides may be coupled to diagnostic or therapeutic moieties including radionuclides, fluorescein, rhodamine as well as others (see page 7). Olsson et al also teach that the HPRG polypeptides may be employed to develop affinity columns (solid support) for the isolation of the HPRG receptor, which is an affinity ligand for binding to or isolating an HPRG-binding molecule (see page 7, paragraph [0074]). Thus, Olsson et al anticipate the claims.

***Conclusion***

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER

RESULT 1
KGHUGH
histidine-rich glycoprotein precursor - human
N;Alternate names: HRG
C;Species: Homo sapiens (man)
C;Date: 04-Dec-1986 #sequence_revision 04-Dec-1986 #text_change 16-Jun-2000
C;Accession: A01287; S29669
R;Koide, T.; Foster, D.; Yoshitake, S.; Davie, E.W.
Biochemistry 25, 2220-2225, 1986
A;Title: Amino acid sequence of human histidine-rich glycoprotein derived from the nuc
A;Reference number: A01287; MUID:86216149; PMID:3011081
A;Accession: A01287
A;Molecule type: mRNA
A;Residues: 1-525 <KOI>
A;Cross-references: GB:AB005803; NID:g2280513; PIDN:BAA21613.1; PID:g2280514
R;Hennis, B.; Havelaar, A.; Kluft, C.
submitted to the EMBL Data Library, October 1991
A;Description: PCR detection of a dinucleotide repeat in the human histidine-rich glyc
A;Reference number; S29669
A;Accession: S29669
A;Status: preliminary
A;Molecule type: DNA
A;Residues: 214-247 <HEN>
A;Cross-references: EMBL:Z17218; NID:g32453; PIDN:CAA78925.1; PID:g32454
C;Comment: Although its physiological function is not yet known, HRG does bind heme, d
din, and the lysine-binding site of plasminogen. On the basis of its homology with HMW
lood coagulation cascade.
C;Comment: The amino half of this protein is homologous to the first two cystatin-like
ould not have inhibitory activity.
C;Comment: In addition to having a high histidine and proline content, this protein ha
e-rich' region.
C;Genetics:
A;Gene: GDB:HRG
A;Cross-references: GDB:120055; OMIM:142640
A;Map position: 3q27-3q27
C;Superfamily: histidine-rich glycoprotein; cystatin homology
C;Keywords: duplication; glycoprotein; heparin binding; tandem repeat
F;1-18/Domain: signal sequence #status predicted <SIG>
F;19-525/Product: histidine-rich glycoprotein #status predicted <MAT>
F;19-131/Domain: cystatin homology <CY1>
F;140-246/Domain: cystatin homology <CY2>
F;276-321/Region: proline-rich
F;348-437/Region: histidine-rich
F;351-497/Region: proline-rich
F;63,125,344,345/Binding site: carbohydrate (Asn) (covalent) #status predicted
F;78-89,105-126,218-241/Disulfide bonds: #status predicted

Query Match 100.0%; Score 966; DB 1; Length 525;
Best Local Similarity 100.0%; Pred. No. 8.8e-75;
Matches 148; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy          1 HPHKHHSHEQHPHGHHPHAHHPHEHDTHRQHPHGHHPHGHHPHGHHPHGHHPHGHHPHCH 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        350 HPHKHHSHEQHPHGHHPHAHHPHEHDTHRQHPHGHHPHGHHPHGHHPHGHHPHGHHPHCH 409

Qy         61 DFQDYGPCDPPPHNQGHCCHGHGPPPGHLRRRGPGKGPRPFHCRQIGSVYRLPPLRKGEV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        410 DFQDYGPCDPPPHNQGHCCHGHGPPPGHLRRRGPGKGPRPFHCRQIGSVYRLPPLRKGEV 469

Qy        121 LPLPEANFPSFPLPHHKHPLKPDNQPFP 148
              ||||||||||||||||||||||||||||
Db        470 LPLPEANFPSFPLPHHKHPLKPDNQPFP 497
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Exhibit A

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RESULT 1
HRG_RABIT
ID   HRG_RABIT      STANDARD;      PRT;   526 AA.
AC   Q28640;
DT   01-NOV-1997 (Rel. 35, Created)
DT   01-NOV-1997 (Rel. 35, Last sequence update)
DT   15-MAR-2004 (Rel. 43, Last annotation update)
DE   Histidine-rich glycoprotein precursor (Histidine-proline rich
DE   glycoprotein) (HPRG) (Fragment).
GN   HRG.
OS   Oryctolagus cuniculus (Rabbit).
OC   Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
OC   Mammalia; Eutheria; Lagomorpha; Leporidae; Oryctolagus.
OX   NCBI_TaxID=9986;
RN   [1]
RP   SEQUENCE FROM N.A., AND SEQUENCE OF 9-23; 301-313 AND 422-429.
RC   TISSUE=Serum;
RX   MEDLINE=96229917; PubMed=8639676;
RA   Borza D.-B., Tatum F.M., Morgan W.T.;
RT   "Domain structure and conformation of histidine-proline-rich
RT   glycoprotein.";
RL   Biochemistry 35:1925-1934(1996).
CC   -!- FUNCTION: The physiological function is not yet known. It binds
CC       heme, dyes and divalent metal ions. It can inhibit rosette
CC       formation and is known to interact with heparin, thrombospondin,
CC       and the lysine-binding site of plasminogen. On the basis of its
CC       homology with HMW kininogen, the His-rich region of this protein
CC       may mediate the contact activation phase of intrinsic blood
CC       coagulation cascade.
CC   -!- SUBCELLULAR LOCATION: Secreted.
CC   -!- TISSUE SPECIFICITY: Expressed by the liver and secreted in plasma.
CC   -!- DOMAIN: In addition to having a high His and Pro content, this
CC       protein has many internal repeats. 15 tandem repetitions of a 5-
CC       residue sequence (G[H/P][H/P]PH, consensus) form a His/Pro-rich
CC       region.
CC   -!- SIMILARITY: Contains 2 cystatin-like domains.
CC   ---------------------------------------------------------------------
CC   This SWISS-PROT entry is copyright. It is produced through a collaboration
CC   between the Swiss Institute of Bioinformatics and the EMBL outstation -
CC   the European Bioinformatics Institute. There are no restrictions on its
CC   use by non-profit institutions as long as its content is in no way
CC   modified and this statement is not removed. Usage by and for commercial
CC   entities requires a license agreement (See http://www.isb-sib.ch/announce/
CC   or send an email to license@isb-sib.ch).
CC   ---------------------------------------------------------------------
DR   EMBL; U32189; AAC48516.1; -.
DR   InterPro; IPR000010; Cystatin.
DR   Pfam; PF00031; cystatin; 1.
DR   SMART; SM00043; CY; 2.
KW   Glycoprotein; Heparin-binding; Repeat; Signal.
FT   NON_TER       1      1
FT   SIGNAL       <1      8       POTENTIAL.
FT   CHAIN         9    526       HISTIDINE-RICH GLYCOPROTEIN.
FT   DOMAIN        9    126       CYSTATIN-LIKE 1.
FT   DOMAIN      127    243       CYSTATIN-LIKE 2.
FT   DOMAIN      251    296       PRO-RICH.
FT   DOMAIN      329    498       PRO/HIS-RICH.
FT   DISULFID     14    505       BY SIMILARITY.
FT   DISULFID     68     79       BY SIMILARITY.
FT   DISULFID     95    116       BY SIMILARITY.
FT   DISULFID    193    415       BY SIMILARITY.
FT   DISULFID    207    230       BY SIMILARITY.
FT   DISULFID    272    302       POTENTIAL.
FT   CARBOHYD    115    115       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    192    192       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    240    240       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    310    310       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   CARBOHYD    485    485       N-LINKED (GLCNAC. . .) (POTENTIAL).
FT   SITE        303    304       CLEAVAGE (BY PLASMIN).
FT   SITE        421    422       CLEAVAGE (BY PLASMIN).
SQ   SEQUENCE   526 AA;  58877 MW;  810F23D367D93D42 CRC64;

  Query Match           100.0%;  Score 697;  DB 1;  Length 526;
  Best Local Similarity 100.0%;  Pred. No. 5.1e-41;
  Matches  101;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy        1 SVNIIHRPPPHGHHPHGPPPHGHHPHGPPPHGHPPHGPPPRHPPHGPPPHGHPPHGPPPH 60
            ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      321 SVNIIHRPPPHGHHPHGPPPHGHHPHGPPPHGHPPHGPPPRHPPHGPPPHGHPPHGPPPH 380

Qy       61 GHPPHGPPPHGHPPHGPPPHGHPPHGHGFHDHGPCDPPSHK 101
            |||||||||||||||||||||||||||||||||||||||||||
Db      381 GHPPHGPPPHGHPPHGPPPHGHPPHGHGFHDHGPCDPPSHK 421
```

Exhibit B

☐ 1: P04196. Reports Histidine-rich gl...[gi:123523]

Exhibit C

```
LOCUS       P04196                  525 aa            linear   PRI 15-JUN-2004
DEFINITION  Histidine-rich glycoprotein precursor (Histidine-proline rich
            glycoprotein) (HPRG).
ACCESSION   P04196
VERSION     P04196  GI:123523
DBSOURCE    swissprot: locus HRG_HUMAN, accession P04196;
            class: standard.
            created: Mar 20, 1987.
            sequence updated: Mar 20, 1987.
            annotation updated: Jun 15, 2004.
            xrefs: gi: 184391, gi: 306888, gi: 2280513, gi: 2280514, gi: 32453,
            gi: 32454, gi: 68793
            xrefs (non-sequence databases): SWISS-2DPAGEP04196, GenewHGNC:5181,
            MIM 142640, InterProIPR000010, PfamPF00031
KEYWORDS    Glycoprotein; Heparin-binding; Repeat; Signal; Polymorphism; Direct
            protein sequencing.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 525)
  AUTHORS   Koide,T., Foster,D., Yoshitake,S. and Davie,E.W.
  TITLE     Amino acid sequence of human histidine-rich glycoprotein derived
            from the nucleotide sequence of its cDNA
  JOURNAL   Biochemistry 25 (8), 2220-2225 (1986)
  MEDLINE   86216149
   PUBMED   3011081
  REMARK    SEQUENCE FROM N.A.
            TISSUE=Liver
REFERENCE   2  (residues 1 to 525)
  AUTHORS   Wakabayashi,S., Takahashi,K., Tokunaga,F. and Koide,T.
  TITLE     Direct Submission
  JOURNAL   Submitted (??-JUL-1997)
  REMARK    SEQUENCE FROM N.A.
REFERENCE   3  (residues 1 to 525)
  AUTHORS   Hennis,B.C., Frants,R.R., Bakker,E., Vossen,R.H., van der
            Poort,E.W., Blonden,L.A., Cox,S., Khan,P.M., Spurr,N.K. and
            Kluft,C.
  TITLE     Evidence for the absence of intron H of the histidine-rich
            glycoprotein (HRG) gene: genetic mapping and in situ localization
            of HRG to chromosome 3q28-q29
  JOURNAL   Genomics 19 (1), 195-197 (1994)
  MEDLINE   94245171
   PUBMED   8188234
  REMARK    SEQUENCE OF 214-247 FROM N.A.
REFERENCE   4  (residues 1 to 525)
  AUTHORS   Hughes,G.J., Frutiger,S., Paquet,N., Ravier,F., Pasquali,C.,
            Sanchez,J.C., James,R., Tissot,J.D., Bjellqvist,B. and
            Hochstrasser,D.F.
  TITLE     Plasma protein map: an update by microsequencing
  JOURNAL   Electrophoresis 13 (9-10), 707-714 (1992)
  MEDLINE   93092937
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   PUBMED   1459097
   REMARK   SEQUENCE OF 19-27.
            TISSUE=Plasma
   COMMENT  ---------------------------------------------------------------------
            This SWISS-PROT entry is copyright. It is produced through a
            collaboration between the Swiss Institute of Bioinformatics and
            the EMBL outstation - the European Bioinformatics Institute.
            The original entry is available from http://www.expasy.ch/sprot
            and http://www.ebi.ac.uk/sprot
            ---------------------------------------------------------------------.
            [FUNCTION] The physiological function is not yet known. It binds
            heme, dyes and divalent metal ions. It can inhibit rosette
            formation and is known to interact with heparin, thrombospondin,
            and the lysine-binding site of plasminogen. On the basis of its
            homology with HMW kininogen, the His-rich region of this protein
            may mediate the contact activation phase of intrinsic blood
            coagulation cascade.
            [SUBCELLULAR LOCATION] Secreted.
            [TISSUE SPECIFICITY] Expressed by the liver and secreted in plasma.
            [DOMAIN] In addition to having a high His and Pro content, this
            protein has many internal repeats. 12 tandem repetitions of a
            5-residue sequence (GHHPH, consensus) form a histidine-rich region.
            [SIMILARITY] Contains 2 cystatin-like domains.
   FEATURES             Location/Qualifiers
        source          1..525
                        /organism="Homo sapiens"
                        /db_xref="taxon:9606"
        gene            1..525
                        /gene="HRG"
        Protein         1..525
                        /gene="HRG"
                        /product="Histidine-rich glycoprotein precursor"
        Region          1..18
                        /gene="HRG"
                        /region_name="Signal"
        Region          16..126
                        /gene="HRG"
                        /region_name="Cystatin-like domain"
                        /note="CY"
                        /db_xref="CDD:14782"
        Region          19..525
                        /gene="HRG"
                        /region_name="Mature chain"
                        /note="Histidine-rich glycoprotein."
        Region          19..136
                        /gene="HRG"
                        /region_name="Domain"
                        /note="Cystatin-like 1."
        Bond            bond(24,504)
                        /gene="HRG"
                        /bond_type="disulfide"
                        /note="By similarity."
        Site            63
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                        /site_type="glycosylation"
                        /note="N-linked (GlcNAc...) (Potential)."
        Bond            bond(78,89)
                        /gene="HRG"
                        /bond_type="disulfide"
                        /note="By similarity."
        Site            87
                        /gene="HRG"
                        /site_type="glycosylation"
                        /note="N-linked (GlcNAc...) (Potential)."
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     Bond            bond(105,126)
                     /gene="HRG"
                     /bond_type="disulfide"
                     /note="By similarity."
     Site            125
                     /gene="HRG"
                     /site_type="glycosylation"
                     /note="N-linked (GlcNAc...) (Potential)."
     Region          137..254
                     /gene="HRG"
                     /region_name="Domain"
                     /note="Cystatin-like 2."
     Region          144..241
                     /gene="HRG"
                     /region_name="Cystatin-like domain"
                     /note="CY"
                     /db_xref="CDD:36"
     Bond            bond(203,417)
                     /gene="HRG"
                     /bond_type="disulfide"
                     /note="By similarity."
     Region          204
                     /gene="HRG"
                     /region_name="Variant"
                     /note="P -> S (in dbSNP:3181917). /FTId=VAR_014528."
     Bond            bond(218,241)
                     /gene="HRG"
                     /bond_type="disulfide"
                     /note="By similarity."
     Region          276..321
                     /gene="HRG"
                     /region_name="Domain"
                     /note="Pro-rich."
     Site            344
                     /gene="HRG"
                     /site_type="glycosylation"
                     /note="N-linked (GlcNAc...) (Potential)."
     Site            345
                     /gene="HRG"
                     /site_type="glycosylation"
                     /note="N-linked (GlcNAc...) (Potential)."
     Region          350..497
                     /gene="HRG"
                     /region_name="Domain"
                     /note="His/Pro-rich."
ORIGIN
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       61 venttvyylv ldvqesdcsv lsrkywndce ppdsrrpsei vigqckviat rhshesqdlr
      121 vidfncttss vssalantkd spvlidffed teryrkqank alekykeend dfasfrvdri
      181 ervarvrgge gtgyfvdfsv rncprhhfpr hpnvfgfcra dlfydveald lespknlvin
      241 cevfdpqehe ningvpphlg hpfhwggher ssttkppfkp hgsrdhhhph kphehgpppp
      301 pderdhshgp plpqgpppll pmscsscqha tfgtngaqrh shnnnssdlh phkhhsheqh
      361 phghhphahh phehdthrqh phghhphghh phghhphghh phghhphchd fqdygpcdpp
      421 phnqghcchg hgpppghlrr rgpgkgprpf hcrqigsvyr lpplrkgevl plpeanfpsf
      481 plphhkhplk pdnqpfpqsv sescpgkfks gfpqvsmfft htfpk
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